

AMENDMENTS TO THE SPECIFICATION

- Please replace the paragraph on page 13, lines 1-5 with the following amended paragraph:

In a further preferred embodiment, the invention provides peptide mimetics (also called peptidomimetics), or non-peptide mimetics designed on the basis of the sequence and/or the structure of a phosphopeptide of the invention. Preferably, such peptidomimetic is not the peptide RNNEFYA-NH₂ (SEQ ID NO:75), Y being a phosphorylated Tyrosine residue.

- Please replace the paragraph on page 13, lines 9-11 with the following amended paragraph:

The invention further relates to functional derivatives of the phosphopeptides of the invention. Preferably, the phosphopeptide is not the peptide RNNEFYA-NH₂ (SEQ ID NO:75), Y being a phosphorylated Tyrosine residue.

- Please replace the paragraph on page 16, lines 10-15 with the following amended paragraph:

The phosphatases inhibited by the phosphopeptides of the invention have been described to be implied in the development of several pathologies. Therefore, the phosphopeptides, mimetics or functional derivatives of the invention, which are specific PTP inhibitors, are used as medicaments in accordance with the present invention. Preferably, such phosphopeptide, mimetic or functional derivative is not the peptide RNNEFYA-NH₂ (SEQ ID NO:75), Y being a phosphorylated Tyrosine residue.

- Please replace the paragraph on page 21, lines 4-27 with the following amended paragraph:

PTPs were cloned and purified as described previously (27). Briefly, specific primers corresponding to the beginning and the end of the catalytic domain of every PTPs were used to amplify by PCR an EST containing the region of interest. These primers were designed with an EcoRI site at the 5' end and a NotI site at the 3' end. These two restriction sites were used to clone the catalytic domain in frame into a pGEX4TK vector (Pharmacia). For the construction of the trapping mutants, we designed

internal primers that create a D to A mutation as described (27). Mutation for the R88 position within PTP-Sap1 was performed using the following internal primers: for 5'ATT GTA GCG GTT CTT GGC GT3' ([SEQ ID NO:79](#)) and 5'ACG CCA AGA ACC GCT ACA ATA ATG TGC TGC CCT ATG ACT G3' ([SEQ ID NO:80](#)). The clones used for SPOT analysis were subcloned into modified pGEX2TK encoding for a PKA phosphorylation site in-frame with GST. Constructs were checked by sequencing. *Escherichia coli* BL21(codon +; Stratagene) were transformed, and a single colony was grown in 25 mL LB + amp + Cm at 37°C until an OD of 0.5 was reached. Protein production was performed at 30°C for 3 hours after the addition of IPTG at 250 µM final concentration. The bacteria were pelleted and resuspended in lysis buffer (50 mM tris pH 8.0, 5 mM EDTA, 0.1% Triton X-100, 150 mM NaCl + a proteinase inhibitor cocktail, Complete™ (Roche Molecular Biochemicals)) and lysed by a treatment with lysozyme (200 µg/ml final) for 1 hour on ice followed by three rounds of sonication. Supernatant of the lysate was incubated for more than 2 hours with 100 µl of a 50% solution of glutathione Sepharose beads (Pharmacia) at 4°C. Finally, beads were extensively washed and the PTPs were eluted in 50 mM Tris pH 8.0 with 10 mM glutathione. Glycerol was added to a final concentration of 20%, amount of proteins produced was determined with Bio Rad protein assay and aliquots were stocked at -20°C until use.

- Please replace the paragraph on page 21, line 28 through page 22, line 5 with the following amended paragraph:

PEP-GST constructs were prepared as follows: the primers used correspond to the pVIII capsid sequence of M13 + two restriction sites (XhoI and NotI): 5'TAT CTC GAG TCT TTC GCT GCT GAG GGT GA3' ([SEQ ID NO:81](#)) for the sense and 5'ATA GCG GCC GCT TGC AGG GAG TCA AAG GCC G3' ([SEQ ID NO:82](#)) for the antisense. The DNA of the phage was directly amplified by adding 10⁹ phages to the PCR mix. After PCR using Herculanase Polymerase (Stratagene), the DNA fragments (100 bp) were purified using Microcon® PCR (Millipore) and gel extraction was performed with Utrafree®-DA (Millipore). The cloning and the protein purification were finally accomplished following the same protocol as for the PTPs, with the only difference that TKB1 (Stratagene) bacteria were transformed and a single colony was grown and induced for protein production and phosphorylation exactly as described by the manufacturer. Again, all constructs were checked by DNA sequencing before protein production.

- Please replace the paragraph on page 23, lines 15-19 with the following amended paragraph:

When an increase in the number of trapped clones was observed, phages were purified as single clones and colony-PCR was performed using phage primers, forward: 5'ATG AAA AAG TCT TTA GTC CTC3' (SEQ ID NO:83) and reverse: 5'CAG CTT GAT ACC GAT AGT TGC3' (SEQ ID NO:84). The PCR products were then purified and sequenced using the same primers. Sequences were read in both directions using SeqmanII Software.

- Please replace the paragraph on page 24, line 27 through page 25, line 11 with the following amended paragraph:

We used the phagemid described in (1) which displays an insert of 9 amino acids at the C-terminus part of the pVIII protein. We wanted to (i) remove the EF motif that corresponds to the EcoRI site on the 5' end of the insert and (ii) add a fixed Tyrosine on the middle of the displayed sequence. The DNA insert was designed with MunI in 5'-end and a BamHI in the 3' end (underlined). The primer was also prolonged with the reverse sequence of pGXb (**bold**) primer for the filling with the polymerase. Thus, the sequence of the synthetic oligonucleotides encoding for ELXXXXYXXXXDP (SEQ ID NO:76) (X means any amino acid) is: 5'-ATA CAA TTG (NNK)₄ TAT (NNK)₃ NNG GAT CCT ACA CAT GCA GCT CCC GGA G (SEQ ID NO:77), where n= A,T,G or C and K= G or T. The method used to construct the library was performed as described in (2, 3). Briefly, 400 pmole of the library primer and pGXb (5'-GTC TCC GGG AGC TGC ATG TG-3') (SEQ ID NO:78) were annealed and the complementary strand was filled using Klenow DNA PolI (New England Biolabs). The DNA was then extracted by a phenol-chloroform precipitation and the product was digested by MunI and BamHI. The mix was then loaded on a 15% polyacrylamide gel with control and the band migrating at the correct size was cut and recovered (4). The insert was cloned into the pC89 vector which had been previously opened with EcoRI and BamHI (1). XL1BlueMRF' electrocompetent cells (Stratagene) were transformed with the ligation and propagated in 20 large plate (100 ml LB-agar with ampicillin and tetracycline). Cells were harvested and frozen in 2 mL aliquots.

- Please insert a copy of the Sequence Listing submitted herewith at the end of the specification, after the abstract.